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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/510,560	02/22/2000	Kenneth Iain Cumming	9701-6	3011

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EXAMINER	
LUNDGREN, JEFFREY S	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
09/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/510,560	CUMMING ET AL.	
	Examiner	Art Unit	
	JEFFREY S. LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 6/13/08.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 258-345 is/are pending in the application.

4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 258-264, 266, 268, 275, 276, 278-279, 283-286, 289, 292, 295-300, 302, 303, 306, 309, 310-314, 316-318, 320, 322, 329, 330, 332, 334, 338-340, 344 and 345 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 265,267,269-274,277,280-282,287,288,290,291,293,294,301,304,305,307,308,315,319,321,323-328,331,333,335-337 and 341-343.

DETAILED ACTION

Election of Species

Applicant's election with traverse of the elected species in the reply filed on June 13, 2008, is acknowledged. The traversal is on the grounds that the Office would not be seriously burdened by the search of the large number of species in claims 258-345 because many of the species are well-known in the art.

While the Examiner agrees that the species in claims do in fact appear to be well-known in the manner they are claimed, that the search of all species would still be overly burdensome. For example, art that relates to certain species is unlikely to relate other species (delayed release formulation compared to an instant release formulation).

The requirement is still deemed proper and is therefore made FINAL.

Status of the Claims

Applicants have canceled all previous claims and introduced new claims 258-345; claims 265, 267, 269-274, 277, 280, 281, 282, 287, 288, 290, 291, 293, 294, 301, 304, 305, 307, 308, 315, 319, 321, 323-328, 331, 333, 335-337 and 341-343 are withdrawn from consideration; claims 258-264, 266, 268, 275, 276, 278-279, 283-286, 289, 292, 295-300, 302, 303, 306, 309, 310-314, 316-318, 320, 322, 329, 330, 332, 334, 338-340, 344 and 345, are the subject of the Office Action below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 258-264, 266, 268, 275, 276, 278-279, 283-286, 289, 292, 295, 296, 302, 303, 306, 309, 310, 316-318, 320, 322, 329, 330, 332, 334, 338-340, 344 and 345, are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts *et al.*, International Patent Application Publication WO 97/05903, published on February 20, 1997, in view of Heiber *et al.*, U.S. Patent No. 5,346,701, issued on September 13, 1994, and optionally any one or more of the following of: Teng *et al.*, U.S. Patent No. 6,747,014 B2, issued on June 8, 2004; Garces *et al.*, U.S. Patent No. 5,736,161, April 7, 1998; and Bachynsky *et al.*, U.S. Patent No. 5,190,748, issued on March 2, 1998.

Although Applicants have amended the claims, Applicants allege the rejection to be improper. Instead of considering the art as a whole, Applicants base their arguments on the claimed inventions, not for everything taught. For example, consider Applicants arguments where Applicants focus on the two component enhancer system in Watts:

> "Both of the Watts et al. embodiments describe the absorption promoter as a two-component mixture in which one component must be a dispersing agent while the other may be either: (1) a medium chain fatty acid or salt; or (2) a mixture of mono/diglycerides of medium chain fatty acids. Clearly, the scope of the disclosure of Watts et al. extends only to the use of two-component absorption promoters. All of the embodiments which employ a medium chain fatty acid or salt thereof in the absorption promoter must also contain a dispersing agent as a second component of the absorption promoter."

Reply filed on March 13, 2008, page 15.

Applicants continue to allege the teaching of Watts is improper, and suggest that Watts only teaches capric acid and sodium caprate (Reply, page 16), and emphasize the differences in the melting points between sodium caprate and capric acid (page 17), and suggest that Watts teaches away from sodium caprate (Reply, page 17).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, Applicants' arguments are selectively focused towards only certain aspects of the teachings of the prior art, and do not consider the art as a whole.

Watts makes quite clear that drugs, such as LMWH, have enhanced systemic absorption from compounds, specifically, sodium caprate:

> "***It has been known for some time that sodium caprate can act as an absorption promoting agent***, probably by the perturbation of membranes or modification of tight junctions between cells (Kajii et al. J. Pharm. Sci. 77 390, 1988)."

Watts, paragraph bridging pages 2 and 3 (emphasis added).

Applicants' attention is also directed towards Figures 1-3 and 11 (especially Figure 3 where the effects of a single enhancer are shown), where it is quite clear that Watts teaches the enhancing effects of sodium caprate on active agents, and clearly contemplates LMWH. This concept is also expressed in Heiber, whom understands the benefits of an enhancer for LMWH. Although Applicants emphasize that their claim uses the closed language "consisting of" to describe their pharmaceutical formulation, it is respectfully pointed out that part c) of their claim adds considerable breadth that it reads on most excipients (*i.e.*, one or more excipients selected from…).

Claim 258 is directed towards a solid oral dosage form which is effective in delivering a drug and an enhancer, each as defined below, to an intestine and which comprises a pharmaceutical composition consisting of:

(A) a therapeutically effective amount of a hydrophilic or macromolecular drug in the form of crystalline and/or amorphous particles;

(B) one or more absorption enhancers, each of which: (i) is a solid at room temperature; (ii) is a salt of a medium chain fatty acid having a carbon length of form 8 to 14 carbon atoms in particulate form; and (iii) is present in the dosage form in a therapeutically effective amount and such that the ratio of the drug to the one or more absorption enhancers is 1:100,000 to 10:1; and

(C) one or more excipients selected from the group consisting of rate-controlling polymeric materials, diluents, lubricants, disintegrants, plasticizers, anti-tack agents, opacifying agents, pigments, and flavorings.

Watts discloses a drug delivery composition (tablet, capsule, including a gelatin capsule, and a pellet) for drug delivery through oral administration (see Abstract; accordingly this is a delayed release formulation) comprising a drug (*e.g.*, oligosaccharide or polysaccharide including low molecular weight heparin (meets the drug limitations of claims 258, 262-264, 266, 275, 276, 289, 302, 316, 317, 318, 320, 329, 330, 334, 338, 339, 340, 344 and 345); see page 8), and an absorption promoter (see page 24; see also Example 10 on page 22 of the PCT). This formulation is a solid at room temperature, as is the enhancer sodium caprate. It is also provided with the auxiliary excipient Labrasol, and without Labrasol, which instead of being an enhancer is considered a dispersing agent (see Detailed Description, see also Example 1-3 on pages 16-18). Watts also teaches the use of a single enhancer with insulin and capric acid (see Figure 3, and description thereof). Watts teaches that the absorption promoter comprises a fatty acid or a salt thereof, where the fatty acid has between 6 and 16 carbon atoms, for example capric acid (Example 10) or its sodium salt, sodium caprate (pages 5, 24; see also claims 1 and 3) which can be used *alone* (meets teaching of claimed limitation of sodium caprate in claims 258, 262, 268, 278, 279, 302, 316, 322, 332, 334 and 340) or in admixture with a fatty acid derivative. For example, Watts states regarding the use of sodium caprate on intestinal absorption of active compounds that are otherwise not readily bioavailable:

> "***It has been known for some time that sodium caprate can act as an absorption promoting agent***, probably by the perturbation of membranes or modification of tight junctions between cells (Kajii et al. J. Pharm. Sci. 77 390, 1988)."

Watts, paragraph bridging pages 2 and 3 (emphasis added).

Watts further teaches that the drug can be chosen from LMWH, and more (pages 8, 11-12, and 24; and claim 6). Watts teaches that the composition is formulated in a capsule (*e.g.*, hard/soft gelatin), tablet (as in claims 260), pellet, or multiparticulate capsule or tablet which is comprised of or coated with a material which is dissolved by the conditions found in the intestines such as "rate-controlling" for enteric release, and comprises a cellulose ester, HPMC at

page 9, lines 14-29 (as in claim), or a methacrylic acid polymer at pages 10-12 (as in claims 259, 261, 283, 284), for *in vivo* therapeutic administration to a patient (see pages 14-15). Such enteric coatings meet the claimed enteric coatings (compare to paragraph 0037 of Applicants' disclosure, *i.e.*, "releases the drug and the enhancer *rapidly* once the *appropriate* site in the intestine has been reached" as in claim 283). Watts teaches sodium caprate and capric acid; both components prepared in a formulation similar to Example 3 would result in all components being a solid at room temperature.

Although Watts teaches tablet dosage forms as well as preparing certain formulations by adding certain mass amounts of active and enhancer, Watts does not explicitly state that the active agent or the enhancer are provided in the form of particles.

Heiber teaches certain formulations that are pressed into tablet form from a dry blend of LMWH and an enhancer (*i.e.*, NaTC):

> "LMWH tablets are prepared in the following manner. ***An active LMWH layer was prepared by dry blending 2.010 g LMWH***, 0.504 g of hydroxypropyl cellulose, (KLUCEL LF) ***and 0.450 g of NaTC***. To this was added 500 µl of 200 proof ethanol and the mixture was wet blended to give a wet granulation having a dough like consistency. The wet granulation was passed through an 18 mesh screen and allowed to dry for 3 hours in a draft oven at 25 °C. The dried granulation was then passed through a 20 mesh screen and placed in a glass vial with 0.030 g of magnesium stearate and 0.006 g of mint flavor and dry blended again. A 100 mg amount of this mixture was filled into a 1/2" diameter die and ***precompressed*** on a Carver Press Model C ***with 0.25 ton pressure*** for a 3 second time dwell time to form the active drug/enhancer/polymer layer."

Heiber, col. 10, lines 25-41. Such a teaching meets the physical form limitations of the independent claims as well as claims 285, 286, and 303. As in claims 292, 295, 296, 306, 309 and 310, Heiber teaches the inert diluent sorbitol (col. 10, lines 42-45).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Watts and Heiber are directed toward providing pharmaceutical dosage forms, such as tablets, for administering pharmaceutically active peptides that have poor absorption characteristics. Watts clearly shows that an oral dosage form comprising insulin has a much increased bioavailability in the presence of the caprate anion in the GIT, and suggests a number of active peptides that this approach is useful for, including

LMWH in the form of a tablet, and specifically with sodium caprate as the enhancer. Heiber teaches a particular tablet formulation that is prepared as a dry blend of LMWH and enhancer particles and is compressed to have a particular tablet shape and size. Although Watts does not explicitly teach a dry blend compression tablet, and Heiber does not teach sodium caprate, arriving at an oral tablet for GIT delivery in the claimed physical form would have been obvious in view Watts and Heiber because the differences between what is claimed and what is taught by Watts and Heiber is considered well-known in the art and/or routine. For example, see Teng, where a pharmaceutical composition of a pressed tablet is prepared from a powder composition of particles comprising sodium caprylate used as an enhancer for improved absorption of an active agent (*i.e.*, an oligonucleotide; Example 15). See Garces, wherein an oral capsule is prepared with LMWH and sodium caprate, and therefore has increased absorption (Example 2). Bachynsky further demonstrates these points, as it is taught that the active agents may take the form of the a liquid formulation or numerous solid formulations:

> "The formulation can be filled into a hard- or soft-shell capsule or, if the formulation is a liquid, absorbed onto a suitable carrier to ***make a free flowing powder*** and then filled into the capsule or, alternatively, ***compressed into a pill or tablet***. Still other possible dosage forms include microcapsule or beadlet forms of the antibacterial compound mixed with the absorption enhancing system which may thereafter be encapsulated in an enteric coated capsule.
>
> ***Usage of enteric coating materials in this manner serves to protect the antibacterial compound from the gastric fluid and to achieve optimum delivery of the antibacterial compound together with the absorption enhancing system to the intestine***. The enteric coating material is, for the most part, resistant to the gastric fluid and is unaffected by it but dissolves in the intestinal fluid to cause release of the drug."

Bachynsky, col. 8, lines 18-50; multiple approaches for delivery through various mucosal membranes, such as oral or rectal administration are also disclosed.

Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Claims 258-264, 266, 268, 275, 276, 278-279, 283-286, 289, 292, 295-300, 302, 303, 306, 309, 310-314, 316-318, 320, 322, 329, 330, 332, 334, 338-340, 344 and 345, are rejected under 35 U.S.C. 103(a), as being unpatentable over Watts *et al.*, International Patent Application

Publication WO 97/05903, published on February 20, 1997, in view of Heiber *et al.*, U.S. Patent No. 5,346,701, issued on September 13, 1994, and optionally any one or more of the following of: Teng *et al.*, U.S. Patent No. 6,747,014 B2, issued on June 8, 2004; Garces *et al.*, U.S. Patent No. 5,736,161, April 7, 1998; and Bachynsky *et al.*, U.S. Patent No. 5,190,748, issued on March 2, 1998, as applied to the listed claims in the rejection above, and further in view of Burk *et al.*, U.S. Patent No. 5,221,734, issued on June 22, 1993.

The limitations of the previously rejected claims and the corresponding teachings of the art is found in the rejection above, and hereby incorporated into the instant rejection.

None of Watts or Heiber explicitly teach the claimed stearic acid lubricant or crospovidone, as in claims 297-300 and 311-314.

Burk teaches certain pharmaceutical compositions for delivering a particular growth factor (i.e., milk growth factor), and discloses tablet formulation and their common excipients. Included in the description are the lubricant stearic acid and the disintegrant crospovidone (col. 11, lines 28-58).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Watts, Heiber and Burk are directed towards the delivery active agents using tablet formulations. Where Watts and Heiber teach certain oral formulations comprising an enhancer and LMWH, and teach tablet formulations, neither reference provides an exhaustive list of common excipients in standard tablet cores containing the active ingredients. However, the claimed compositions directed towards the stearic acid lubricant and disintegrant crospovidone, as taught by Burk, are common and well-known excipients for standard/instant release tablets, having predictable results that are commensurate in scope with the claims (e.g., tablet, or an enterically coated tablet). Therefore, the invention as a whole was *prima facie* obvious at the time it claimed.

Common Ownership of Claimed Invention Presumed

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Conclusions

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL

/JD Schultz, PhD/
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